REMARKS

The Office Action mailed 30 November 2009, has been received and its contents carefully noted. Claims 1, 2, 4-9 and 21 were pending and claims 1, 2, 4-9 and 21 were rejected. Reconsideration in view of the following is respectfully requested.

Interview Summary

Applicants appreciate the Examiner taking the time to conduct a personal interview on 18 February 2010. During the interview, Applicants explained that Chotai only looks at the methylation state of one specific site which is much like assaying a single nucleotide polymorphism (SNP) for designating whether one has a given disease and that the other cited documents mention nothing about analyzing unmethylated fragments. Applicants explained that prior to the present invention, it was believed that unmethylated sequences do not provide any useful information as an array/profile. Thus, the prior art is concerned with chewing up the unmethylated fragments in order to only "see" the methylated and hypermethylated fragments.

Applicants explained that the instant invention, as claimed, results in a plurality of unmethylated fragments which, as a whole (i.e. array/profile), unexpectedly provides useful information.

The Examiner indicated that he would favorably receive an affidavit which provides probative evidence that the information obtained from the claimed method provides unexpected results, i.e. unmethylated fragments that are more informative than expected.

Again, Applicants greatly appreciate the Examiner's time and thoughtful consideration.

The Claimed Invention

Prior to the present invention, the conventional wisdom in the art was that only methylated and hypermethylated fragments provided useful information. Thus, prior to the present invention, those skilled in the art analyzed aimed to "chew up" unmethylated fragments in order to obtain only methylated and hypermethylated fragments for further analysis.

In spite of the conventional wisdom in the art, the present inventors discovered that the unmethylated fraction of one or more nucleotide sequences can provide significantly more useful

information than what was expected.

Thus, the present invention, as set forth in claim 1, is directed to a method of obtaining an unmethylated fraction from a nucleotide sequence by conducting the digestion steps in a specific order, i.e.

1. First, the unmethylated sequences of the nucleotide sequence are cut (step b));

2. Then, the ends of the cut sequences are ligated together to form ligated sequences (step c)); and

3. Then methylated sequences of the ligated sequences are cut (step d)).

This specific order of digestion steps results in an unmethylated fraction which comprises a plurality of unmethylated fragments which is then analyzed.

The invention as set forth in claim 21 is directed to comparing the unmethylated sequences of a test (disease) sample with that of a control (normal) sample.

Claim Rejections Under 35 U.S.C. 103(a)

The Examiner rejected claims 1 and 4-9 under 35 U.S.C. 103(a) as being unpatentable over Yan (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (US 6,605,432) in view of Chotai (J Med Genet. 1998 Jun;35(6):472-5). The Examiner rejected claim 2 as being unpatentable over Yan or Huang in view of Chotai and further in view of Dean (US 6,617,137). The Examiner rejected claim 21 as being unpatentable over Yan or Huang in view of Dean.

Applicants understand the Examiner's rejections to be based upon his assertion that Chotai provides the reason as to why one of ordinary skill in the art would have been motivated to rearrange the order of the digestion steps of Yan or Huang in order to obtain an unmethylated sequence for analysis.

Applicants respectfully submit that a prima facie case of obviousness has not been established. Specifically, the cited documents, alone or in combination, do not specifically teach or suggest the specific order of the steps as set forth in the claims which results in an unmethylated fraction (i.e. a plurality of unmethylated fragments) which is analyzed and/or the advantages of analyzing a plurality of unmethylated fragments.

In support, Applicants respectfully submit a 132 Declaration by Dr. David I. Martin who

has extensive education and experience in the epigenetics field.

As provided at #12 of the Declaration, Dr. Martin states that it is his opinion that one or ordinary skill in the art would not have been motivated to combine and/or modify the disclosures of Yan, Huang, Chotai and Dean in order to obtain an unmethylated fraction, i.e. a plurality of unmethylated fragments, as claimed, because Yan, Huang and Dean do not teach or suggest that unmethylated fragments should be retained or analyzed and Chotai is directed to the analysis of the methylated state of a single genetic locus, the SNRPN locus, in order to distinguish Prader-Willi syndrome (PWS) from Angelman syndrome (AS). As set forth in Figure 1 of Chotai, unmethylated SNRPN is indicative of PWS and methylated SNRPN is indicative of AS. Dr. Martin states that Chotai relates to a situation dealing with imprinted loci which are normally found in either a methylated state or an unmethylated state. Imprinted loci are known to be special cases which are not representative of a genome as a whole. Chotai does not mention anything about any other genetic locus or loci and their methylation states. Nowhere does Chotai teach or suggest that a plurality of unmethylated fragments obtained from one or more nucleotide sequences will likely provide information about whether a subject suffers from PWS or AS.

Dr. Martin states at #13 that conventional wisdom prior to the claimed invention was that only methylated and hypermethylated DNA fragments provided useful information such that, in his opinion, those skilled in the art at the time of the invention would have been taught to only enrich and analyze the methylated fraction of DNA (and would have been taught against enriching the unmethylated fraction).

Thus, Applicants respectfully submit that in view of the fact that the cited documents do not mention anything about analyzing a plurality of unmethylated fragments and conventional wisdom, one of ordinary skill in the art would not have been motivated to combine and modify the disclosures of the cited documents in order to obtain and analyze an unmethylated fraction according to the instant invention with a reasonable likelihood of success in obtaining any useful information.

In addition, Applicants respectfully submit that the present invention provides unexpected superior results. Specifically, as set forth in paragraph [0094] of the specification and as

provided in Schumacher et al. (Nucleic Acids Research 2006, 34(2):528-542) (enclosed), analysis of the unmethylated fraction in and around the COMT gene results in over 400 informative fragments whereas analysis of the hypermethylated fraction provides only 6 informative fragments. Nowhere do the cited documents, alone or in combination, teach or suggest that an unmethylated fraction will provide more than about 66X more informative fragments than that of a methylated fraction.

In support, at #14, Dr. Martin states that, in his opinion, one of ordinary skill in the art would not, at the time of the invention, have had any reason to believe that the unmethylated fraction would provide significantly more informative fragments than the methylated fraction as the understanding in the field was that aberrant hypermethylation of specific loci was linked to disease and it was known that the majority of CpG sites in genomic DNA are methylated rather than unmethylated.

At #15, Dr. Martin states that, in his opinion, one of ordinary skill in the art would have found it unexpected and surprising that unmethylated fractions can provide significantly more informative fragments than hypermethylated fractions. Thus, at #16, Dr. Martin is of the opinion that the claimed invention provides superior and unexpected results which are not taught or suggested by the cited documents, alone or in combination.

In view of the lack of any disclosure which would lead one of ordinary skill in the art to obtain and analyze the profile of a plurality of unmethylated fragments with a reasonable expectation of success in obtaining useful information and the unexpected superior result that an unmethylated fraction provides significantly more informative fragments than that obtained from a methylated fraction, Applicants respectfully submit that the claimed invention is unobvious.

Therefore, the rejections under 35 U.S.C. 103(a) should properly be withdrawn.

Request for Interview

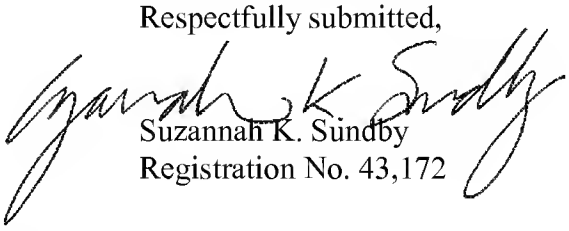
Either a telephonic or an in-person interview is respectfully requested should there be any remaining issues.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Therefore, it is respectfully requested that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Official action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. 1.136(a), and any fees required therefor are hereby authorized to be charged to **Deposit Account No. 024300**, Attorney Docket No. **034263.002**.

Respectfully submitted,



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